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Review

HIV, Tat and dopamine transmission

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ABSTRACT

Human Immunodeficiency Virus (HIV) is a progressive infection that targets the immune system, affecting more than 37 million people around the world. While combinatorial antiretroviral therapy (cART) has lowered mortality rates and improved quality of life in infected individuals, the prevalence of HIV associated neurocognitive disorders is increasing and HIV associated cognitive decline remains prevalent. Recent research has suggested that HIV accessory proteins may be involved in this decline, and several studies have indicated that the HIV protein transactivator of transcription (Tat) can disrupt normal neuronal and glial function. Specifically, data indicate that Tat may directly impact dopaminergic neurotransmission, by modulating the function of the dopamine transporter and specifically damaging dopamine-rich regions of the CNS. HIV infection of the CNS has long been associated with dopaminergic dysfunction, but the mechanisms remain undefined. The specific effect(s) of Tat on dopaminergic neurotransmission may be, at least partially, a mechanism by which HIV infection directly or indirectly induces dopaminergic dysfunction. Therefore, precisely defining the specific effects of Tat on the dopaminergic system will help to elucidate the mechanisms by which HIV infection of the CNS induces neuropsychiatric, neurocognitive and neurological disorders that involve dopaminergic neurotransmission. Further, this will provide a discussion of the experiments needed to further these investigations, and may help to identify or develop new therapeutic approaches for the prevention or treatment of these disorders in HIV-infected individuals.

Contents

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1. Introduction

There have been a number of excellent reviews detailing the effects of HIV-1 Tat on the CNS, and a growing body of research suggests that HIV infection specifically damages and/or dysregulates the dopaminergic system in the CNS (Cass et al., 2003; Czub et al., 2004; Ferris et al., 2008; Fitting et al., 2015; Gaskill et al., 2013; Gaskill et al., 2014; Koutsilieri et al., 2004; Purohit et al., 2011). A number of recent studies suggest that these changes to the dopaminergic system specifically involve Tat; therefore, this review will focus specifically on the Tat protein and its effect on dopaminergic neurotransmission. This review will briefly discuss both the pathogenesis of HIV in the CNS and dopamine neurotransmission in the brain, and then review what is known about the Tat protein itself. This will be followed by discussion of the model systems used to explore the effects of Tat on the dopaminergic system, the direct effects of Tat on neuropathogenesis and the brain regions implicated in Tat modulation of cognitive function. The review will then explore the direct impact of Tat on the dopamine transporter and on the dopamine receptors. Finally, the discussion will briefly discuss the specific impact of Tat on the dopaminergic effects of psychostimulants, as well as other drugs of abuse. Although the impact of Tat on neuropathogenesis has been covered at length recently (Dahal et al., 2015; Hauser and Knapp, 2014; Maubert et al., 2015; Mediouni et al., 2015a), these sections will provide a distinct viewpoint on the subject, focusing specifically on the potential synergistic effects of Tat and drug abuse on dopaminergic neurotransmission.

2. HIV Neuropathogenesis

Globally, approximately 37 million people are infected with the human immunodeficiency virus. In 2014, more than 1.2 million people died as a result of this infection (UNAIDS, 2015). HIV is a lentivirus which principally targets the immune system, primarily infecting CD4 + T-cells, macrophages and monocytes. Untreated, HIV infection progressively destroys the immune system, leading to the development of acquired immunodeficiency syndrome (AIDS) (Derdeyn and Silvestri, 2005; Moir et al., 2011; Stevenson, 2003). The development of combinatorial antiretroviral therapy (cART) has successfully reduced rates of death and improved length and quality of life (UNAIDS, 2015; Weber et al., 2013), transitioning HIV infection from a terminal to a chronic diagnosis (Deeks et al., 2013). This success has increased the prevalence of HIV, particularly among vulnerable populations, such as drug abusers (El-Bassel et al., 2014). Currently, the prevalence of HIV is 22 times higher among injection drug users than among the general population (Beyrer et al., 2010; Crime, 2014; Mathers et al., 2008) and even the use of non-injection drugs greatly increases the risk of acquiring HIV (Kipp et al., 2011). The mechanism(s) by which different types of drugs of abuse increase the risk of acquiring or exacerbating HIV is not clear, and understanding these processes is critical, as drug abuse exacerbates the development of AIDS in both the periphery and in the central nervous system (CNS) (Baum et al., 2009; Lucas et al., 2006). The direct effects of HIV infection on the reward pathway and drug-seeking behavior are not fully understood, but numerous studies have suggested HIV affects the dopaminergic system (Aylward et al., 1993; Berger et al., 1994; Chang et al., 2008; Itoh et al., 2000; Jenuwein et al., 2004; Kieburtz et al., 1991; Nath et al., 2000; Obermann et al., 2009a; Sardar et al., 1996; Scheller et al., 2010; Wang et al., 2004).

While a majority of studies on HIV focus on the effects on the peripheral immune system, infection of the CNS is a growing health concern. HIV enters the CNS rapidly following initial infection (Davis et al., 1992; Valcour et al., 2012). Infection of the CNS leads to a constellation of neurocognitive impairments, including cognitive dysfunction, behavioral changes, motor deficits, and dementia, that are currently known as HIV-associated neurocognitive disorders (HAND) (Antinori et al., 2007; Navia et al., 1986; Price et al., 1988; Sacktor et al., 2002; Simioni et al., 2010). Prior to the implementation of cART (combinatorial antiretroviral therapy, then called HAART) in 1996, around 16% of HIV-infected individuals manifested HIV encephalitis (Davies et al., 1998), and between 5 and 20% were diagnosed with HIV-associated dementia (HAD) (Janssen et al., 1989; Maschke et al., 2000; McArthur et al., 1994; Sacktor, 2002). With cART, the more severe neurological manifestations have become rare (Ellis et al., 2007; Heaton et al., 2010a; Joska et al., 2010; Sacktor, 2002), but 40–70% of infected individuals still suffer from HAND (Cysique et al., 2004; Heaton et al., 2010a; Heaton et al., 2011a; Simioni et al., 2010; Tozzi et al., 2005). Further, the prevalence of HAND is increasing as these individuals have longer life expectancy (Brew and Chan, 2014; Heaton et al., 2010b; Simioni et al., 2010). HAND is still found among individuals with viral suppression (Heaton et al., 2011b; Robertson et al., 2007), which suggests that factors other than viral replication are involved. A number of studies indicate that drug abuse may exacerbate both the neuropathogenesis of HIV and the neurocognitive impact of infection in both cART-naïve and cART-treated individuals (Chana et al., 2006; Langford et al., 2003b; Meade et al., 2011a; Meyer et al., 2014; Nath, 2010; Starace et al., 1998). However, other studies show that drug abuse does not increase he neurological deficits induced by HIV infection (Basso and Bornstein, 2003; Byrd et al., 2011b; Grassi et al., 1995); hence, the precise impact of drug abuse on HIV neuropathogenesis remains unclear.

HIV is thought to enter the brain primarily by using infected monocytes as “Trojan Horses” to move across the blood-brain barrier (Izquierdo-Useros et al., 2010; Kim et al., 2003; Peluso et al., 1985). Within the brain, the monocytes mature into macrophages and produce new HIV virions, spreading the infection throughout the brain. In the CNS, HIV primarily infects perivascular macrophages and microglia (Gonzalez-Scarano and Martin-Garcia, 2005; Joseph et al., 2015; Kure et al., 1990). The presence of HIV has also been shown in astrocytes both in vitro (Eugenin and Berman, 2007) and *in vivo* (Churchill et al., 2009; Tornatore et al., 1994), but the mechanism of entry into these cells, and the overall role of astrocytes in HIV neuropathogenesis remains unclear (Gray et al., 2014; Joseph et al., 2014; Luo and He, 2015). Infected cells, primarily macrophages, monocytes and microglia produce and secrete a variety of inflammatory host and viral factors, including cytokines, chemokines and viral proteins. These factors result in chronic neuroinflammation and neurotoxicity, which are thought to be central to the development and persistence of HAND (Gannon et al., 2011; Gill et al., 2012; Hong and Banks, 2015; Kraft-Terry et al., 2009; Zayyad and Spudich, 2015).

3. The transactivator of transcription (Tat)

Among the neurotoxic viral proteins released by infected cells is the viral protein Tat (Chang et al., 1997; Ensoli et al., 1993; King et al., 2006; Rayne et al., 2010a). Tat is short for trans-activator of transcription, and is required for the successful transcription of full-length HIV mRNA. This protein is one of the first genes expressed in the HIV replication cycle. The viral mRNA of Tat consists of two exons. The first exon is comprised of amino acids 1–72, and contains the transcriptional functions of the protein. The second exon, comprised of amino acids 73–101 or amino acids 73–86, houses the integrin binding domains. The longer form of Tat (~101 aa) is far more common and is found in the majority of HIV clinical isolates, while the shorter form of Tat (~86 aa) is mostly found in laboratory adapted strains and is the result of a single nucleotide polymorphism in the second exon which creates a stop codon (Campbell et al., 2005; Jeang, 1996; Jeang et al., 1999). Perhaps due to the prevalence of this premature stop codon in the laboratory-adapted, clade B strains of HIV that are common in North America and Western Europe, the shorter form of Tat is much more commonly used in research. Some studies examining multiple forms of Tat have shown functional differences between the shorter and wild type forms of Tat (Bertrand et al., 2013; Campbell et al., 2005), while others do not find such differences (Ma and Nath, 1997). Thus, the effects of wild-type